more activity than the cognate, wild-type protein; and (d) expressing the selected variant regulator protein in a cell, thereby increasing production of the secondary metabolite in the cell.

In certain embodiments of the fourth aspect, the cell is a fungal cell. In certain embodiments of the fourth aspect, the protein regulator of secondary metabolite production is a transcription factor. In certain embodiments of the fourth aspect, the protein regulator of secondary metabolite production is a transmembrane transporter, a protein that mediates secretion, a kinase, a G-protein, a cell surface receptor, a GTPase activating protein, a guanine nucleotide exchange factor, a phosphatase, a protease, a phosphodiesterase, a bacterial protein toxin, an importin, an RNA-binding protein, an SCF complex component, an adherin, or a protein encoded within a biosynthetic cluster. In certain embodiments of the fourth aspect, the cell is a heterologous cell, preferably selected from the group consisting of *S. cerevisiae, E. coli, A. nidulans, Candida sp.*, and *N. crassa*. In certain other embodiments of the fourth aspect, the cell is a homologous cell, preferably selected from the group consisting of *Aspergillus sp., Penicillium sp., Acremonium chrysogenum, Yarrowia lipolytica, Nodulisporium sp., Fusarium sp., Monascus sp., Claviceps sp., Trichoderma sp., Tolypocladium sp., Tricotheicium sp., Fusidium sp., Emericellopsis sp., Cephalosporium sp., Cochliobolus sp., Helminthosporium sp., Agaricus brunescens, Ustilago maydis, Neurospora sp., Pestalotiopsis sp.*, and *Phaffia rhodozyma*.

In certain other embodiments of the fourth aspect, the cell is a heterologous cell and the method further comprises expressing the variant regulator protein in a homologous cell, thereby increasing secondary metabolite production in the homologous cell. In certain embodiments thereof, the heterologous cell is an organism selected from the group consisting of *S. cerevisiae, E. coli, A.*

nidulans, *Candida sp.*, , and *N. crassa* and the homologous cell is an organism selected from the group consisting of *Aspergillus sp.*, *Penicillium sp.*, *Acremonium chrysogenum*, *Yarrowia lipolytica*, *Nodulisporium sp.*, *Fusarium sp.*, *Monascus sp.*, *Claviceps sp.*, *Trichoderma sp.*, *Tolypocladium sp.*, *Tricotheicium sp.*, *Fusidium sp.*, *Emericellopsis sp.*, *Cephalosporium sp.*, *Cochliobolus sp.*, *Helminthosporium sp.*, *Agaricus brunescens*, *Ustilago maydis*, *Neurospora sp.*, *Pestalotiopsis sp.*and *Phaffia rhodozyma*.

In a fifth aspect, the invention provides an isolated variant regulator protein of secondary metabolite production having increased activity compared to a cognate, wild-type protein, made by the process comprising: (a) selecting a nucleic acid comprising a polynucleotide encoding a protein regulator of secondary metabolite production; (b) mutating the nucleic acid to create a plurality of nucleic acid molecules encoding variant regulator proteins of secondary metabolite production; (c) selecting a variant regulator protein with more activity than the cognate, wild-type protein; and (d) recovering the selected variant regulator protein.

In certain embodiments of the fifth aspect, the variant regulator protein selected has more activity in a fungal cell. In certain embodiments of the fifth aspect, the protein regulator of secondary metabolite production is a transcription factor. In certain embodiments of the fifth aspect, the protein regulator of secondary metabolite production is a transmembrane transporter, a protein that mediates secretion, a kinase, a G-protein, a cell surface receptor, a GTPase activating protein, a guanine nucleotide exchange factor, a phosphatase, a protease, a phosphodiesterase, a bacterial protein toxin, an importin, an RNA-binding protein, an SCF complex component, an adherin, or a protein encoded within a biosynthetic cluster. In certain embodiments of the fifth aspect, the variant regulator protein selected has

more activity in a heterologous cell, preferably selected from the group consisting of *S. cerevisiae, E. coli, A. nidulans, Candida sp., Neurospora sp., Pestalotiopsis sp.,* and *N. crassa.* In certain embodiments of the fifth aspect, the variant regulator protein selected has more activity in a homologous cell, preferably selected from the group consisting of *Aspergillus sp., Penicillium sp., Acremonium chrysogenum, Yarrowia lipolytica, Nodulisporium sp., Fusarium sp., Monascus sp., Claviceps sp., Trichoderma sp., Tolypocladium sp., Tricotheicium sp., Fusidium sp., Emericellopsis sp., Cephalosporium sp., Cochliobolus sp., Helminthosporium sp., Agaricus brunescens, Ustilago maydis, Neurospora sp., Pestalotiopsis sp.,* and *Phaffia rhodozyma.*

In certain embodiments of the fifth aspect, the variant regulator protein selected has more activity in a homologous cell and a heterologous cell. In embodiments thereof, the heterologous cell is an organism selected from the group consisting of *S. cerevisiae, E. coli, A. nidulans, Candida sp., Neurospora sp., Pestalotiopsis sp.,* and *N. crassa* and the homologous cell is an organism selected from the group consisting of *Aspergillus sp., Penicillium sp., Acremonium chrysogenum, Yarrowia lipolytica, Nodulisporium sp., Fusarium sp., Monascus sp., Claviceps sp., Trichoderma sp., Tolypocladium sp., Tricotheicium sp., Fusidium sp., Emericellopsis sp., Cephalosporium sp., Cochliobolus sp., Helminthosporium sp., Agaricus brunescens, Ustilago maydis, Neurospora sp., Pestalotiopsis sp.,* and *Phaffia rhodozyma.*

In yet another embodiment of the fifth aspect, the variant regulator protein is a variant protein of the lovE protein having at least one of the following mutations: (1) a Group 6 amino acid residue mutated to a Group 2 amino acid residue at position 31, for example, the mutation represented by F31L;(2) a Group 3 amino acid residue mutated to a Group 5 amino acid residue at position 41, for example, the mutation represented by Q41K